Medication Policy Manual

Policy No: dru282

Topic: Kyprolis®, carfilzomib

Date of Origin: September 24, 2012

Committee Approval Date: July 15, 2016

Next Review Date: July 2017

Effective Date: August 1, 2016

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Carfilzomib is an intravenous medication that is used in the treatment of multiple myeloma when front-line therapies have not been effective (salvage therapy setting).

Policy/Criteria

I. Most contracts require prior authorization approval of carfilzomib prior to coverage. Carfilzomib may be considered medically necessary in patients with multiple myeloma when criteria A and B below are met:

A. Documentation of a diagnosis of recurrent multiple myeloma.

AND

B. At least one prior therapy for recurrent multiple myeloma has been ineffective or not tolerated (see *Appendix 1*). This prior therapy must have included one of the following medications unless both are contraindicated:

1. Bortezomib.

OR

2. An immunomodulator (lenalidomide or thalidomide).

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx does not consider carfilzomib to be a self-administered medication.

B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Carfilzomib is considered not medically necessary when used in combination with pomalidomide (Pomalyst).

IV. Carfilzomib is considered investigational when used for all other conditions, including but not limited to:

A. First-line therapy for multiple myeloma

B. Waldenström's macroglobulinemia

Position Statement

- Carfilzomib is a proteosome inhibitor used in the treatment of recurrent multiple myeloma when at least one to three front-line therapies have not been effective (salvage therapy setting). It is administered intravenously as a single agent or in combination with dexamethasone +/- lenalidomide.
- Carfilzomib has been shown to be safe and effective when used in the treatment of multiple myeloma after failure of at least one prior therapy. In clinical trials the majority of patients had received prior treatment with bortezomib-based or immunomodulator-based (lenalidomide or thalidomide) therapy.
- The combination of carfilzomib plus lenalidomide and dexamethasone have been studied in multiple myeloma in patients who had failed one to three prior therapies. The combination was shown to improve progression free survival and overall response rate compared to lenalidomide and dexamethasone alone.

- The efficacy of carfilzomib was based on overall response rate, a surrogate marker that has not been shown to correspond to improved survival or symptom control.
- Carfilzomib may cause serious side effects including fatigue, anemia, low platelets, cardiac toxicity, and peripheral neuropathy. Its safety has not been evaluated relative to other therapies.
- Evidence for carfilzomib in the first-line multiple myeloma setting and for the treatment of Waldenström's macroglobulinemia are preliminary. Additional higher quality clinical studies are needed to support the safety and effectiveness in these settings.
- There is currently no published evidence to support the safety and efficacy of carfilzomib in other conditions.

Clinical Efficacy

- Carfilzomib has not been shown to provide a clinical benefit such as improved survival or symptom control, and it has not been directly compared to placebo or any active comparator.
- Approval of carfilzomib was based on one single-arm trial in 266 subjects that evaluated overall response rates in patients with relapsed multiple myeloma. [1]
    * Patients enrolled in the trial had received at least two prior therapies (including bortezomib (Velcade) and an immunomodulator [lenalidomide (Revlimid) or thalidomide (Thalomid)].
    * The median number of prior therapies was five and 95% were refractory to their last line of therapy.
    * Evaluation of efficacy was based on overall response rate (ORR), a surrogate marker that has not been validated to correspond to a clinical outcome such as improved survival.
    * The study reported an ORR of 23.7% (17.7% partial responses, 4.9% very good partial response, and 0.4% complete response).
    * There is low confidence in the evidence from the study because a cause effect relationship cannot be established due to the lack of comparator.
- A single large, randomized, open-label trial evaluated the combination of carfilzomib plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone (control group) in subjects with relapsed multiple myeloma. Subjects enrolled in the trial had between one and three prior therapies.[2]
    * The median progression free survival (PFS) was 26.3 months and 17.6 months (hazard ratio of 0.69 with a $p = 0.001$) in the carfilzomib (Kyprolis) and control arm, respectively. Corresponding ORRs were 87.1 and 66.7%.
    * Although a lower HR for death was observed in the treatment group (HR 0.79, $p = 0.04$), OR survival data is not mature; the durability and clinical meaningfulness of this difference is not fully elucidated.
    * There is low confidence in these data due to high attrition (~30%) and lack of blinding. Although improvements in ORR and PFS were observed, they have not been shown to correlate to clinical outcomes such as overall survival.

- The National Comprehensive Cancer Network (NCCN) multiple myeloma guideline lists Carfilzomib in combination with lenalidomide and dexamethasone as a category 1 (highest) recommendation. There are multiple alternate category 1 recommended treatments (see Appendix 1). Carfilzomib in combination with lenalidomide and dexamethasone is also listed as a non-preferred, category 2A recommendation for the treatment of multiple myeloma in patients who are transplant candidates with progressive solitary plasmacytoma or smoldering myeloma (asymptomatic) that has progressed to active (symptomatic) myeloma. [3]
- There is a small, preliminary (phase I/II), uncontrolled trial evaluating the combination of carfilzomib, lenalidomide, and dexamethasone in multiple myeloma. Larger, controlled studies are needed to establish the safety and efficacy of this combination. [3]
- There are no published trials that study carfilzomib in any other condition.

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN clinical practice guidelines.

OTHER CANCER SETTINGS AND CONDITIONS

- There is insufficient evidence to support the use of carfilzomib for the first line treatment of MM. Two small, uncontrolled, open-label trials evaluated carfilzomib (Kyprolis)-based regimens in subjects with newly diagnosed multiple myeloma. Although complete responses were noted in approximately 20% to 33% of patients in both trials, neither response rate or progression free survival have been shown to accurately predict clinical outcomes in multiple myeloma. Well-designed studies are necessary to establish efficacy and benefit in these populations [4,5]
- There is currently insufficient evidence to support the use of carfilzomib in combination with rituximab and dexamethasone for the treatment of Waldenström's macroglobulinemia. Although it is listed in NCCN guidelines as a category 2A recommendation, the only information to date consists of a single-center, uncontrolled phase II study in 31 patients. Well-designed studies are necessary to establish efficacy and benefit in these populations. [6]

Safety [7]

- The most common adverse events (incidence of > 30%) reported in the carfilzomib (Kyprolis) trial included fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia.
- Serious adverse events, some which have resulted in death, include cardiac toxicity (cardiac arrest, heart failure and myocardial infarction), pulmonary toxicity (pulmonary hypertension), hepatic failure, and renal toxicity. Peripheral neuropathy, cell lysis syndrome, and infusion reactions have also been reported.
- There are no studies that directly compare the safety of carfilzomib with other medications.

Appendix 1: Salvage Therapies Used in the Treatment of Recurrent Multiple Myeloma (Note: A therapy may consist of a multi-drug regimen)
NCCN Category 1 Recommendations:
Bortezomib
Bortezomib/liposomal doxorubicin
Carfilzomib/lenalidomide/dexamethasone
Elotuzumab/lenalidomide/dexamethasone
Ixazomib/lenalidomide/dexamethasone
Lenalidomide/dexamethasone
Panobinostat/bortezomib/dexamethasone
Pomalidomide/dexamethasone
NCCN Category 2A Recommendations:
Repeat Primary Induction Therapy (if relapse at > 6 months)
Bendamustine
Bortezomib/cyclophosphamide/dexamethasone
Bortezomib/dexamethasone
Bortezomib/lenalidomide/dexamethasone
Bortezomib/thalidomide/dexamethasone
Bortezomib/vorinostat
Carfilzomib
Carfilzomib/dexamethasone
Cyclophosphamide
Cyclophosphamide/lenalidomide/dexamethasone
Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)
DT-PACE + bortezomib (VTD-PACE)
High-dose cyclophosphamide
Ixazomib
Ixazomib/dexamethasone
Lenalidomide/bendamustine/dexamethasone
Panobinostat/carfilzomib
Thalidomide/dexamethasone

Cross References
Pomalyst®, pomalidomide, Medication Policy Manual, Policy No. 293
Revlimid®, lenalidomide, Medication Policy Manual, Policy No. 127
Velcade®, bortezomib, Medication Policy Manual, Policy No. 190

Codes	Number	Description
HCPCS	J9047	Injection, carfilzomib, 1 mg

References

1. Siegel, DS, Martin, T, Wang, M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. United States, 2012. p. 2817-25.
2. Stewart, AK, Rajkumar, SV, Dimopoulos, MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *The New England journal of medicine*. 2015 Jan 8;372(2):142-52. PMID: 25482145
3. Treon, SP, Tripsas, CK, Meid, K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenstrom's macroglobulinemia. United States, 2014. p. 503-10.
4. Bringhen, S, Petrucci, MT, Larocca, A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. *Blood*. 2014;124:63-9. PMID: 24855212
5. Sonneveld, P, Asselbergs, E, Zweegman, S, et al. Phase 2 study of carfilzomib, thalidomide, and dexamethasone as induction/consolidation therapy for newly diagnosed multiple myeloma. *Blood*. 2015;125:449-56. PMID: 25398935
6. NCCN Clinical Practice Guidelines in Oncology™. Multiple Myeloma v.3.2016. [cited 6/21/2016]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.
7. Kyprolis® [package insert]. South San Francisco, CA: Onyx Pharmaceuticals, Inc.; January 2015.

Revision History

Revision Date	Revision Summary
07/15/2016	No changes to coverage criteria with this annual update.